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1. Your reference	GWS/24287 01	
2. Patent application number *(The Patent Office will fill in this part)*	0218724.3	12 AUG 2002
3. Full name, address and postcode of the or of each applicant *(underline all surnames)*	Resolution Chemicals Limited Wedgwood Way Stevenage Hertfordshire SG1 4QT	
Patents ADP number *(if you know it)*	4165429001	
If the applicant is a corporate body, give the country/state of its incorporation	Great Britain	
4. Title of the invention	Solvent-based sterilisation of pharmaceuticals.	
5. Name of your agent *(if you have one)*		
"Address for service" in the United Kingdom to which all correspondence should be sent *(including the postcode)*	MATHYS & SQUIRE 100 Gray's Inn Road London WC1X 8AL United Kingdom	
Patents ADP number *(if you know it)*	1081001	

6. If you are declaring priority from one or more earlier patent applications, give the country and the date of filing of the or of each of these earlier applications and *(if you know it)* the or each application number	Country	Priority application number *(if you know it)*	Date of filing *(day / month / year)*
	GB	0203912.1	19 February 2002

7. If this application is divided or otherwise derived from an earlier UK application, give the number and the filing date of the earlier application	Number of earlier application	Date of filing *(day / month / year)*

8. Is a statement of inventorship and of right to grant of a patent required in support of this request? *(Answer 'Yes' if:* *a) any applicant named in part 3 is not an inventor, or* *b) there is an inventor who is not named as an applicant, or* *c) any named applicant is a corporate body.* *See note (d))*	YES

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Continuation sheets of this form	
Description	
Claim(s)	10
Abstract	4
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Priority documents	-
Translations of priority documents	-
Statement of inventorship and right to grant of a patent *(Patents Form 7/77)*	-
Request for preliminary examination and search *(Patents Form 9/77)*	-
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11. I/We request the grant of a patent on the basis of this application.

Signature Mathys & Squire Date

MATHYS & SQUIRE 12 August 2002

12. Name and daytime telephone number of person to contact in the United Kingdom

George W Schlich - 020 7830 0000

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SOLVENT-BASED STERILISATION OF PHARMACEUTICALS

The present invention concerns a method for the sterilisation of drugs, in particular suspensions of drugs intended for use in nebulizers.

Previously it was acceptable for drugs intended for use in nebulizers to be prepared under "clean" conditions. Recently, however, the US FDA has implemented a requirement for all nebulizer solutions to be sterile.

In the light of the US FDA decision it is necessary to produce sterile suspension drugs in the US. This is emphasised by problems which have resulted from the use of "clean" suspensions. Multidose formulations made under "clean" conditions were previously acceptable in the US. However such formulations have caused fatalities in the US due to contamination.

Drugs typically provided as nebule suspensions are the steroids Fluticasone and Budesonide, used to treat asthma and chronic obstructive pulmonary disorder. These drugs are very insoluble in water and are sold as non-sterile powders.

A method of sterilising dry, powdered budesonide is known from International Publication Number WO 99/25359. The method of sterilisation requires budesonide powder to be sterilised and then be mixed with the other components of the formulation under sterile conditions. The drug formulation is subsequently made up under sterile conditions. This method does not permit the complete formulation to be sterilised immediately prior to dispensing into the final sterile vessel.

The sterilisation of suspensions raises particular problems. The desired biological activity of the formulation commonly requires that the diameter of particles of the drug lies within a narrow range (typically less than 5 micrometres). The standard

means of sterilisation, that is the raising of the temperature of the formulation to 121°C for 15 minutes, frequently destroys one or more of the components of the formulation. In addition this treatment results in the clumping or agglomeration of the drug particles in the suspension such that the efficacy of the resulting product is impaired or abolished.

Known alternative methods for the sterilisation of pharmaceuticals are inappropriate for sterilizing suspension formulations of drugs. Pharmaceuticals may be sterilised by passage though a filter having a pore size of not more than 0.2μm. However this cannot be used in the case of many suspensions as the required particle size in these formulations is significantly greater than this filter pore size. Similarly, pharmaceuticals may generally be sterilised by gamma-irradiation, but budesonide, for example, is destroyed by such treatment. No further methods for the sterilisation of pharmaceuticals are currently acceptable to regulatory agencies.

An object of the present invention is to provide an alternative and/or an improved method for sterilization of suspensions of pharmaceuticals.

Accordingly, the present invention provides a method for preparing a sterile composition of a pharmaceutical compound comprising combining solvent with a non-sterile pharmaceutical compound to yield a sterile pharmaceutical compound, optionally removing all or part of the solvent, and under sterile conditions combining the compound with a pharmaceutically acceptable carrier. In one aspect of the invention, the pharmaceutically acceptable carrier may comprise sterile water.

Hence, in use of the invention sterilization may be achieved by combining solvent with the previously non-sterile material. Optional other processing steps may be added, such as filtration as described in more detail below.

By 'combining with', it is meant that solvent may be added to the compound to be sterilised, or vice-versa. Where solvent is added to the compound, solvent may be

added drop-wise or all at once.

By sterile, it is meant that resultant pharmaceutical composition meets the requirements of sterility set by medicine regulatory authorities, such as the MCA in the UK or the FDA in the US, and typically the final bio-burden of such compositions is less than 10 CFU/100ml.

In a particular embodiment the non-sterile pharmaceutical compound is a powder, for instance a micronised powder. This powder can be mixed with a solvent, forming a combination in which the effect of the solvent is to sterilize the active agent. A steroid in powdered form may be sterilized in this way and particular examples include budesonide or fluticasone.

Where the steroid to be sterilised is Budesonide, it is preferred to carry out all processing steps under conditions of low light and low oxygen, in order to avoid degradation of Budesonide.

Generally, any solvent with the required properties may be used in the invention either singly or in combination. It is particularly preferred that the solvent comprises an alcohol. Most particularly preferred is ethyl alcohol, since this solvent is already approved for pharmaceutical formulations for delivery to the lungs. Other alcohols, such as methyl alcohol and isopropyl alcohol, and non-alcohol solvents such as ethyl acetate and TBME may also be used. In order to avoid drug degradation such as hydrolysis of ketal groups, anhydrous, or minimal water content, solvents are preferred.

Good results have been obtained by combining solvent with the compound at an elevated temperature, suitably from 20°C below the boiling point of the solvent up to its boiling point. This can increase the amount of compound that dissolves and may decrease the dissolving time. Solvent can be combined with compound at reflux.

In an alternative aspect of the invention, the combining of solvent and compound to be sterilised is carried out at room temperature. To aid dissolving of the compound in the solvent, however, it may be advantageous to heat the solvent. In one embodiment of the present invention, the solvent is heated to 30-50°C. Good results have been obtained using solvent heated to about 40°C.

In one aspect of the invention sufficient solvent is used to obtain a slurry of the compound. Hence, there is insufficient solvent to form a solution of the compound, nevertheless sterilization is achieved. An advantage is that only a small quantity of solvent is used and where a minimal amount of solvent is tolerated in the final composition, the solvent added for the purpose of sterilization need not be removed to meet the criteria for acceptance of the final composition for pharmaceutical use.

Where solvent is removed from the sterilized composition, solvent is typically removed under reduced pressure, preferably under vacuum conditions, and preferably at a temperature of 40°C or less. Following evaporation, typically only a few ppm of solvent will remain. If the solvent used is ethyl alcohol, it may be an option to omit this evaporation step, although this is dependent on the final concentration present and maximum allowed levels set by the regulatory bodies. If a non-approved solvent is used, it may be essential to remove all solvent from the final composition.

In a particular embodiment, removing solvent yields a solvent-free, sterile powder, suitable for further processing in a sterile line or for packaging and disposal in this sterile form.

In an alternative aspect of the invention, sufficient solvent is used to dissolve the compound, thus obtaining a solution of the compound. For example, 15 or more volumes of 96% ethanol may be used to dissolve budesonide and 60 or more volumes to dissolve fluticasone.

Optionally, the solution is filtered. The purpose of filtration is as a further sterilisation

step and to remove any biomass. Removal of non-viable biomass from the final formulation may not be essential - many pharmaceutical formulations undergo terminal sterilisation, without further filtering. If, therefore, the required level of sterility can be obtained simply by addition of solvent, the filtration step may be unnecessary. Omitting the filtration step would also avoid the expense of replacing clogged filter membranes for every batch of drug solution prepared. In cases where addition of solvent results in incomplete sterilization the addition of a filtration step has the benefit of completing the sterilization.

It is an option for the filter, if present, to be sterile. A filter having a pore size of 0.2μm or less is preferred.

In a yet further aspect of the invention, the sterile pharmaceutical compound is combined with water to form a suspension. If a sterile solution of the pharmaceutical compound is combined with water, the particles will precipitate out of solution to form a suspension. Alternatively, a sterile powder can be added directly to water.

The water will typically be sterile filtered and contain surfactant, such as polysorbate containing compounds, especially Tweens 20 and 80.

It is also an option to remove solvent from the suspension. This solvent may be residual from a sterile powder or may be present within the solution before it is combined with water. Solvent is typically removed from the suspension under reduced pressure, preferably under vacuum conditions and preferably at a temperature of 40°C or less.

In order to be effective in the lungs, the particle size of the active ingredient, Fluticasone and Budesonide in specific embodiments of the invention, must be within a certain size range, and is likely to need to be reduced following preparation of a sterile composition as described. Hence, a still further aspect of the invention comprises treating the suspension to obtain a particle size distribution having a mass

mean diameter in the range 1-5μm, most preferably 2-3μm. The sterile suspension may, for instance, be passed through a microfluidiser to reduce the average mass median diameter of the particles. The microfluidiser is preferably pre-sterilised to avoid contamination of the sterile suspension. A suitable device, referred to as a Microfluidizer(®), is available from Microfluidics, Inc., described in WO 99/07466.

Further treatments of the sterile suspension can include diluting the suspension with sterile water and/or adding excipients such as EDTA and sodium citrate, so as to obtain the end-product pharmaceutical formulation. Excipients can also be added at an earlier stage, e.g. prior to evaporating solvent or at the same time as adding surfactant.

The sterile composition is then typically stored in sterile containers, most preferably ampoules. In use of the invention, the ampoules are nebules. Preferably, the nebules are pre-sterilised and of the blow-fill-seal type.

The invention further provides a method for preparing a sterile composition of a pharmaceutical compound comprising combining solvent with a suspension of a non-sterile pharmaceutical compound to yield a sterile suspension of a pharmaceutical compound, removing solvent, and under sterile conditions combining the sterile suspension with a pharmaceutically acceptable carrier. In one embodiment of the invention, the pharmaceutically acceptable carrier may comprise sterile water.

The volume of solvent required to sterilise an aqueous suspension of drug will generally be greater than for sterilisation of a dry powder, therefore thorough evaporation from the suspension is required. Other preferred features of this method are as for the above-described methods of the invention.

The invention also provides a sterile composition of a pharmaceutical compound prepared by combining solvent with a non-sterile pharmaceutical compound to yield a sterile pharmaceutical compound, optionally removing all or part of the solvent, and

under sterile conditions combining the compound with a pharmaceutically acceptable carrier.

A sterile composition may be a suspension or a powder.

The invention further provides an apparatus for preparing a sterile composition of a pharmaceutical compound, comprising a container defining a sterile inner compartment, a first vessel containing a solvent, and a second vessel containing a non-sterile pharmaceutical compound, arranged so that the solvent can be combined with the non-sterile compound to yield a sterile compound within the compartment, the compartment also containing a sterile aqueous solution into which the sterile compound can be introduced to form a sterile suspension, optionally an apparatus for alteration of the particle size distribution of the suspension and further optionally a sterile exit line for transfer of sterile suspension to sterile ampoules.

The apparatus may further comprise a sterile filter. Good results have been obtained when the sterile filter of the apparatus has a pore size of 0-2μm or less.

The invention is now illustrated in specific embodiments by way of the following example.

<u>Example 1</u>

<u>Sterilisation of budesonide</u>

Powdered Budesonide was dissolved in 15 volumes of 96% alcohol, at reflux. The resultant hot solution was poured through a sterile Pall filter of pore size 0.2 μm to remove any biomass. 5 litres of sterile water/ Tween 80 concentrate were added per litre of filtered drug solution, causing drug particles to precipitate out of solution, forming a suspension.

Evaporation of solvent from the suspension was then carried out at 40°C, under vacuum conditions. An equal volume of water was removed to ensure residual alcohol was kept to a minimum. Residual alcohol concentration was measured and the drug particle size distribution determined.

The concentrated suspension was passed though a microfluidiser, using a 100μm head, in order to reduce the average drug particle size to a mass mean diameter of 2-3μm. Heads of gauge 110μm, 87μm and 75μm "Y" and/or "Z" type may also be used, depending on the desired final particle size. The microfluidised suspension was diluted with sterile water - 1 litre suspension being made up to 500 litres - and combined with EDTA and sodium citrate, as excipients for the final formulation. Standard, pre-sterilised nebules were filled with diluted drug suspension and sealed ready for use.

Example 2

Alternative sterilisation method for Budesonide

Budesonide (36g) was dissolved in de-gassed, pre-heated (35-40°C) 96% ethanol (1:08 litres, 28 volumes) under nitrogen and protected from light at all times. A clear solution of Budesonide was obtained and added drop-wise to a sterile-filtered aqueous solution (2.7 litres, 75 volumes) containing 0.53%w/v Tween-80/ 0.26%w/v EDTA, at such a rate that would maintain a steady distillation of ethanol during the high vacuum. Distillation was carried out (30°C maximum pot temperature, 40°C maximum jacket temperature, 30-35 mb). A splash head was fitted to the flask as a precaution to avoid product being carried over in the possible event of foaming.

Upon completion of addition, the contents were stripped down to a volume of 750ml. Further water (500ml) was added before distilling down to a final volume of 30-35 volumes (1.25 litres, 34.7 volumes in this example) with respect to Budesonide input.

The slurry was then transferred to an amber flask using minimal water to rinse the

distillation flask (100ml used in this example). This was then transferred to a Microfluidizer®, rinsing the flask with any remaining water (90ml in this experiment) required to achieve a total volume of 40 volumes with respect to Budesonide input, thus yielding a concentrated Budesonide suspension.

Example 3

Further alternative sterilisation method for Budesonide

Ethanolic Budesonide solution was obtained as described in Example 2.

Ethanolic Budesonide solution was sterile filtered into the Tween/water at atmospheric pressure prior to any distillation. Upon completion of filtration, (there may be in addition a small alcohol wash) a suspension of Budesonide in approximately 103 volumes alcohol/water/Tween-80 was obtained.

Distillation was commenced at 30°C maximum pot temperature (40°C maximum jacket temperature) and 62 volumes of alcohol/water were removed from the system to leave 41 volumes of water plus a small amount of alcohol. 25 volumes of water were sterile filtered into the batch and removed by vacuum distillation under the same temperature conditions. A further 25 volumes of water were sterile filtered into the batch and the process repeated to leave 41 volumes of a sterile suspension of Budesonide in water/Tween.

The concentrated Budesonide suspension was then microfluidised to a particle size of mass median diameter 2-3μm.

The concentrated, microfluidised Budesonide suspension was then transferred to the final filling tank and flushed through with enough sterile water to ensure complete transfer of batch. At this stage the additional excipients, namely EDTA, sodium citrate, citric acid, and sodium chloride, were sterile filtered into the system and flushed into the final product tank and the tank was made up to 600L with sterile

water. The final concentrations of the excipients in the formulation were as follows:

Tri-sodium citrate	0.5g/L	0.05%w/v
Citric acid	0.28g/L	0.028%w/v
Sodium chloride	8.5g/L	0.085%w/v
EDTA di-sodium salt	0.1g/L	0.01%w/v
Tween-80	0.2g/L	0.02%w/v

The diluted Budesonide suspension was then transferred to sterile ampoules.

CLAIMS

1. A method for preparing a sterile composition of a pharmaceutical compound comprising combining solvent with a non-sterile pharmaceutical compound to yield a sterile pharmaceutical compound, optionally removing all or part of the solvent, and under sterile conditions combining the compound with a pharmaceutically acceptable carrier.

2. A method according to Claim 1 wherein the non-sterile pharmaceutical compound is a powder.

3. A method according to Claim 2 wherein the powder is a micronised powder.

4. A method according to any of Claims 1 to 3 wherein the compound is a steroid.

5. A method according to Claim 4 wherein the compound is budesonide or fluticasone.

6. A method according to any of Claims 1 to 5 wherein the solvent comprises an alcohol.

7. A method according to any of Claims 1 to 6, comprising combining solvent with the compound at an elevated temperature, suitably from 20°C below the boiling point of the solvent up to its boiling point.

8. A method according to Claim 7 wherein the solvent is at reflux.

9. A method according to any of Claims 1-6 wherein the solvent is at 30-50°C.

10. A method according to any of Claims 1 to 9, comprising using sufficient solvent to obtain a slurry of the compound.

11. A method according to any of Claims 1 to 10, comprising removing solvent under reduced pressure.

12. A method according to any of Claims 1-11, comprising removing solvent to yield a solvent-free powder.

13. A method according to any of Claims 1 to 12, comprising using sufficient solvent to obtain a solution of the compound.

14. A method according to Claim 13 comprising filtering the solution.

15. A method according to Claim 14 using a filter having a pore size of 0.2μm or less.

16. A method according to any of Claims 1 to 15, comprising combining the sterile pharmaceutical compound with water to form a suspension.

17. A method according to Claim 16, wherein the water contains surfactant.

18. A method according to Claim 16 or 17, comprising removing solvent from the suspension.

19. A method according to Claim 18, wherein solvent is removed under reduced pressure.

20. A method according to any of Claims 16 to 19, comprising treating the suspension to obtain a particle size distribution having a mass median diameter in the range 1-5μm.

21. A method according to Claim 20, comprising storing the sterile composition in sterile containers.

22. A method according to Claim 21, comprising storing the sterile composition in sterile ampoules.

23. A method for preparing a sterile composition of a pharmaceutical compound comprising combining solvent with a suspension of a non-sterile pharmaceutical compound to yield a sterile suspension of a pharmaceutical compound, removing solvent, and under sterile conditions combining the sterile suspension with a pharmaceutically acceptable carrier.

24. A method according to Claim 23, wherein the compound is a steroid.

25. A method according to any of Claims 23 to 24, wherein the solvent comprises an alcohol.

26. A method according to any of Claims 23 to 25, comprising combining solvent with the compound at an elevated temperature, suitably not less than 20°C below its boiling point.

27. A method according to any of Claims 23-25, wherein solvent is at 30-50°C.

28. A method according to any of Claims 23 to 27, comprising removing solvent under reduced pressure.

29. A method according to any of Claims 23 to 28, wherein the suspension contains a surfactant.

30. A method according to any of Claims 23 to 29, comprising treating the

suspension to obtain a particle size distribution having a mass median diameter in the range 1-5μm.

31. A method according to Claim 30, comprising storing the sterile suspension in sterile containers.

32. A method according to Claim 31, comprising storing the sterile suspension in sterile ampoules.

33. A sterile composition prepared according to the method of any of Claims 1-32.

34. A sterile composition according to Claim 33 wherein the composition is a suspension.

35. A sterile powder prepared according to any of Claims 1 to 12.

36. Apparatus for preparing a sterile composition of a pharmaceutical compound, comprising a container defining a sterile inner compartment, a first vessel containing a solvent, and a second vessel containing a non-sterile pharmaceutical compound, arranged so that the solvent can be combined with the non-sterile compound to yield a sterile compound within the compartment, the compartment also containing a sterile aqueous solution into which the sterile compound can be introduced to form a sterile suspension, optionally an apparatus for alteration of the particle size distribution of the suspension and further optionally a sterile exit line for transfer of sterile suspension to sterile containers.

37. Apparatus according to Claim 36, further comprising a sterile filter.

38. Apparatus according to Claim 37, wherein the sterile filter has a pore size of 0-2μm or less.

SOLVENT-BASED STERILISATION OF PHARMACEUTICALS

ABSTRACT

A method for preparing a sterile composition of a pharmaceutical compound comprising combining solvent with a non-sterile pharmaceutical compound and filtering to yield a sterile pharmaceutical compound, optionally removing all or part of the solvent, and under sterile conditions combining the compound with a pharmaceutically acceptable carrier.